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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/421,778	Applicant(s) FULLER, JAMES T.	
	Examiner Quang Nguyen	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *9,10,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-17 and 20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed January 29, 2002 in Paper No. 13 has been entered.

Claims 1-27 are pending in the present application. Claims 9-10 and 18-19 are withdrawn from further consideration since they are drawn to non-elected inventions.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Election/Restrictions

Applicant's election with traverse the invention of Group I in Paper Nos. 9 and 13 is acknowledged. The traversal is on the ground(s) that the Office has not confirmed whether or not the elected Group I claims encompass both types of particle delivery techniques, namely the deliveries of the nucleic acid construct and particles coated with the same nucleic acid construct. Examiner confirms that Group I claims encompass both types of deliveries.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 102

Claims 1, 7, 12-14 and 25-27 remain rejected under 35 U.S.C. 102(b) as being anticipated by Hofmann et al. (Proc. Natl. Acad. Sci. 93:5185-5190, 1996) for the same reasons set forth in the previous Office Action.

The claims are drawn to a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence, a vector comprising the same nucleic acid construct, and a method of obtaining expression in mammalian cells of a polypeptide of interest using the same. Claims 13 and 14 are drawn to the same method wherein the minimal promoter sequence consists essentially of a hCMV immediate early promoter sequence, a pseudorabies virus early promoter sequence, a simian cytomegalovirus immediate early promoter sequence or a functional variant thereof, and wherein the minimal promoter sequence consists essentially of the sequence spanning positions 0 to –118 of the hCMV immediate early promoter region or a functional variant of the said spanning sequence, respectively. It is noted that the scope of claim 1 and its dependent claims encompasses both *in vitro* and *in vivo* methods of obtaining expression in mammalian cells of an antigen of interest.

With respect to an *in vitro* method, Hofmann et al. disclosed a recombinant retroviral vector construct (SIN-RetroTet vector) containing an autoregulatory cassette comprising a heptamerized tet operator sequence $(TetO)_7$ fused to the human CMV immediate early minimal promoter $P_{hCMV*-1}$ (See Fig. 1). Analysis of transduced C57BL/6 primary myoblasts revealed that the construct yields low basal levels of gene expression and induction of one to two orders of magnitude. In this instant, beta-galactosidase is the polypeptide of interest. The human CMV immediate early minimal promoter $P_{hCMV*-1}$ falls within the scope of a functional variant, the disclosure of Hofmann et al fulfilled the required elements in the claims. With respect to the limitation recited in claims 14 and 22, "consisting essentially of the sequence spanning positions 0

to 118 of the hCMV.....or a functional variant of the said spanning sequence", the claim reads over the P_{hCMV-1} promoter disclosed by Hofmann et al. for which the instant specification has no written support for. Thus, the reference anticipates the instant claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on January 29, 2002 in Paper No. 13 (pages 15-16) have been fully considered.

Applicants mainly argued that Hofmann does not teach a nucleic acid construct comprising a minimal promoter sequence linked to a coding sequence for **an antigen** of interest, and at best Hofmann teaches an *in vitro* method for expressing β-galactosidase. Therefore, Hofmann can not anticipate the instant claims.

Applicants' arguments are found unpersuasive because the instant claims read over the teachings of Hofmann. It is noted that the scope of claim 1 and its dependent claims encompasses both *in vitro* and *in vivo* methods of obtaining expression in mammalian cells of an antigen of interest. β-galactosidase is an antigen as evidenced by the teachings of Raz et al. (Proc. Natl. Acad. Sci. 93:5141-5145, 1996). Upon injection of a plasmid DNA encoding β-galactosidase in Balb/c mice, preferential induction of a Th1 immune response and inhibition of specific IgE antibody formation against β-galactosidase were obtained. It should be further noted that as defined by the instant specification, an antigen refers to any agent, generally a macromolecule, which can elicit an immunological response in an individual (page 7, lines 7-8).

Accordingly, claims 1, 12-14 and 25-27 remain rejected for the reasons set forth above.

Claims 24-27 remain rejected under 35 U.S.C. 102(e) as being anticipated by Gu et al. (U.S. Patent No. 6,200,751).

The claims are drawn to a purified, isolated minimal promoter sequence, a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen of interest, a vector comprising the same nucleic acid construct, preferably a plasmid.

Gu et al. disclosed the isolation and uses of the minimal promoter of the endothelial cell protein C binding protein, EPCR, operably linked to a gene coding for a protein of interest in expression vectors, including plasmid vectors, e.g. pEGFP1 (See col. 4, lines 24-36, lines 45-47; example 3, col. 5, lines 42-49 and the claims). According to Molecular Biotechnology text book (Glick, B.R. & Pasternak, J.J., eds., 1994), a "promoter" is defined as a segment of DNA to which RNA polymerase attaches. It usually lies upstream of (5' to) a gene. A promoter sequence aligns the RNA polymerase so that transcription will initiate at a specific site (page 475). While "enhancer" is defined as a DNA sequence that increases the transcription of a eukaryotic gene when they are both on the same DNA molecule. Also called enhancer element, enhancer sequence (page 461). As such, the promoter including a region resulting in selective expression in endothelial cells, between –1 and –220 based on the positions relative to the ATG encoding the first amino acid of the murine EPCR protein

disclosed by Gu et al. (col. 1, lines 58-63, col. 4, lines 24-36) meets the limitation of the "minimal promoter" of the instant invention which merely requires a promoter sequence without its endogenous enhancer. The encoded green flurorescent protein in the pEGFP1 is an antigen because it is capable of inducing a host immune response in an individual that normally does not naturally habor said gene product. As defined by the instant specification, an antigen refers to any agent, generally a macromolecule, which can elicit an immunological response in an individual (page 7, lines 7-8). Therefore, Gu et al. anticipate the instant claimed invention.

It is noted that the same teachings are disclosed in WO98/20041 (IDS, AT-1).

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on January 29, 2002 in Paper No. 13 (pages 18-20) have been fully considered.

Applicants mainly argued that Gu's "minimal promoter" (-220 to –1) does not meet the limitation of the term "minimal promoter" as defined by the presently claimed invention since Gu reveals that the (-220 to –1) promoter region contains transcription control elements required for constitutive expression in endothelial cells (specifically, the region of the promoter from –220 to –177). Examiner respectfully finds Applicants' argument to be unpersuasive because the region of the promoter from –220 to –177 is not an enhancer. There is no evidence of record indicating that this region (–220 to –177) is an enhancer. The region merely is required <u>for an endothelial cell specific expression</u>. According to Molecular Biotechnology text book (Glick, B.R. & Pasternak,

J.J., eds., 1994), an "enhancer" is defined as a DNA sequence that increases the transcription of a eukaryotic gene when it is on the same DNA molecule with a promoter. Accordingly, Gu's promoter (-220 to –1) is qualified as a minimal promoter as defined by Applicants as an "enhancerless promoter sequence". Moreover, it is noted that as recited in the claims, a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen is not limited to a nucleic acid construct consists of a minimal promoter sequence operably linked to a coding sequence for an antigen as contemplated by Applicant because of the opening language "comprising". Therefore, as written the claims also read over a nucleic acid construct containing other regulatory sequences including enhancers in addition to a "minimal promoter".

Therefore, claims 24-27 remain rejected under 35 U.S.C. 102(e) as being anticipated by Gu et al. for the reasons set forth above.

Following is a new ground of rejection.

Claim Rejections - 35 USC § 112

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of obtaining expression in mammalian cells of an antigen of interest, which method comprises transferring into said cells a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said coding sequence is expressed in said

mammalian cells, and wherein the construct is delivered directly into a subject by injection, intradermal particle delivery, inhalation, topically, intranasally or transmucosally, does not reasonably provide enablement for the same method wherein the construct is delivered directly into a subject by orally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses by exemplification the construction of Hepatitis B surface antigen (HbsAg) expression cassettes driven by full-length or minimal promoter systems (with or without enhancer, respectively) derived from simian CMV, human CMV and pseudorabies virus (PRV). The DNA constructs were coated onto gold carrier particles and administered to Balb/c mice using a particle-mediated delivery technique. Analysis of anti-HbsAg antibodies in sera taken from vaccinated mice six weeks later, revealed that minimal promoter system gave a significant improvement in antibody titer over the fully enhanced promoter system.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claim which encompasses a method of obtaining expression in mammalian cells of an antigen of interest by delivering orally the nucleic acid construct of the presently claimed invention into a subject. The instant specification is not enabled for this particular embodiment of the claim. This is because the nucleic acid construct (naked form or in a coated particle) would be subjected to degradation prior to being transferred to the appropriate cells for expression and induction of a desired immune response. As an example, how would a nucleic acid

molecule remain intact in the low luminal pH of a stomach, or in an oral cavity in the presence of DNA degrading enzymes, such that a transferring of an intact nucleic acid construct could be made into a mammalian cell *in vivo* to mediate the expression of an antigen of interest in a sufficient amount to elicit a host immune response that has any beneficial use. An extensive search of the prior art at the effective filing date of the present application does not reveal that an oral delivery of a naked nucleic acid construct into a subject would be routine and/or effective for inducing any desired host immune response. Therefore, it is incumbent upon the instant specification to provide such guidance. It is further noted that the present application does not provide any guidance for a skilled artisan on how to formulate the nucleic acid construct in any form (apart from coating the nucleic acid construct on carrier particles), so that an oral delivery of such a nucleic acid formulation would be effective for eliciting a desired host immune response to an antigen of interest. With the lack of guidance provided by the present disclosure, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issue raised above, and the breadth of the claim, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Respons to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on January 29, 2002 in Paper No. 13 (pages 7-8) have been fully considered.

Applicant basically argued that Examiner has not provided any reference to support the above assertion, and therefore the rejection must be withdrawn. Examiner respectfully finds Applicant's argument to be unpersuasive. This is because Examiner has set forth a basis for doubting that an oral delivery of a nucleic acid construct would be effective for obtaining an expression of an antigen of interest in mammalian cells for induction of a host immune response contemplated by Applicants, based on scientific reasoning. Furthermore, an extensive search of the prior art at the effective filing date of the present application does not reveal that an oral delivery of a naked nucleic acid construct into a subject would be routine and/or effective for inducing any desired host immune response. Applicant has not provided any factual evidence to indicate otherwise.

Accordingly, claim 3 is rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-8, 11-14 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 2-8, 11-14 and 27, the article "A" beginning each dependent claim renders these claims indefinite. This is because it is unclear whether a specific method of claim 1 and which one or every method within the scope of claim 1 is claimed. Therefore, the metes and bounds of these dependent claims can not be clearly determined. To obviate this rejection, an article - - The - - should be used instead of "A" for the dependent claims. Similarly, claim 27 is rejected for the same reason because of the article "A".

Claim 6 is indefinite because it is dependent upon itself, and there is no steps recited for a method. The metes and bounds of the claim can not be determined.

Claim Rejections - 35 USC § 102

Claims 1-4, 7-8, 11-12, 15-17, 20, 23 and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnston et al. (U.S. Patent No. 6,194,389; IDS, AK-1) as evidenced by Miwa et al. (Mol. Cell. Biol. 7:2803-2813, 1987).

The claims are directed to a method of obtaining expression in mammalian cells of an antigen of interest, which method comprises transferring into said cells a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said coding sequence is expressed in said mammalian cells, coated particles comprising carrier particles coated with the same nucleic acid construct, a particle accelerating device loaded with the same coated particles and the same nucleic acid construct .

Johnston et al. disclose a method for obtaining a protective immune response in a vertebrate subject by *in situ* microprojectile bombardment by providing microprojectiles carrying a DNA sequence comprising in the 5' to 3' direction a regulatory element functional in the tissue cells and a gene positioned downstream of the regulatory element and under the transcriptional control thereof, the gene coding for a protective immune response-producing protein or polypeptide, wherein the microprojectiles comprise a material selected from the group consisting of metal (gold, tungsten, iridium), glass, silica, ice , polyethylene, polycarbonate, graphite and diamond; then accelerating the microprojectiles at the subject using a microprojectile acceleration cell transformation apparatus (See abstract, the claims and particularly col. 5 and 6). Johnston et al. teach that the regulatory sequences which may be used to provide transcriptional control of the gene in the polynucleic acid sequence are generally promoters which are operable in the target tissue cells, and that other regulatory elements which may optionally be incorporated into the polynucleic acid sequence include enhancers, termination sequences and others (col. 5, lines 42-45 and lines 65-67). The polynucleic acid sequence carried by the microprojectile is a recombinant construct of a gene and a regulatory element, which can be in the form of a plasmid (col. 4, lines 37-51). Exemplary promoters that Johnston et al. specifically teach include the human alpha-actin promoter of Miwa and Kedes (Mol. Cell Biol. 2803, 1987), the human beta-actin promoter, the troponin T gene promoter, the human heat shock protein 70 promoter, the metallothionin gene promoter among others. Additionally, exemplary of genes that code for proteins or peptides which produce an immune

response are genes encoding for subunit vaccines against enteroviruses, surface antigen of the hepatitis B (col. 5, lines 4-14). Miwa and Kedes (Mol. Cell Biol. 2803, 1987) teach a promoter region of the human alpha-cardiac actin gene (an upstream region from the transcription initiation site to –177 base pair) that lacks an enhancer element (see abstract), and therefore the disclosed promoter of Miwa and Kedes is a minimal promoter as defined by Applicants as an "enhancerless promoter sequence" (see specification page 4, lines 7-8). Furthermore, it is noted that as recited in the claims, a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen is not limited to a nucleic acid construct consists of a minimal promoter sequence operably linked to a coding sequence for an antigen as contemplated by Applicant because of the opening language "comprising". Therefore, as written the claims also read over a nucleic acid construct containing other regulatory sequences including enhancers in addition to a "minimal promoter".

Accordingly, the teachings of Johnston et al. meet every limitation of the claims, and therefore Johnston et al. anticipate the instant claimed invention as evidenced by Miwa and Kedes.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on January 29, 2002 in Paper No. 13 (pages 16-18) have been fully considered.

Applicants mainly argued that Johnston et al. do not teach the truncation or excision of enhancer sequences from the promoter systems described in their

disclosure, and therefore Johnston et al. can not anticipate the presently claimed invention. Examiner respectfully finds Applicants' argument to be unpersuasive because Johnston et al. clearly teach the use of the human alpha-actin promoter disclosed by Miwa and Kedes in the article Mol. Cell Biol. 2803, 1987 as one of the promoters in a polynucleic acid sequence (can be in the form of a plasmid) carried by the microprojectiles, and that Miwa and Kedes (Mol. Cell Biol. 2803, 1987) disclose a promoter region of the human alpha-cardiac actin gene (an upstream region from the transcription initiation site to –177 base pair) that lacks an enhancer element (see abstract), and therefore the promoter of Miwa & Kedes is qualified as a minimal promoter as defined by Applicants as an "enhancerless promoter sequence". Moreover, it is noted that as recited in the claims, a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen is not limited to a nucleic acid construct consists essentially of a minimal promoter sequence operably linked to a coding sequence for an antigen as contemplated by Applicant because of the opening language "comprising". Therefore, as written the claims also read over a nucleic acid construct containing other regulatory sequences including enhancers in addition to a "minimal promoter".

Accordingly, claims 1-4, 7-8, 11-12, 15-17, 20, 23 and 25-27 are rejected for the reasons set forth above.

Claims 1, 12, 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Burns et al. (Blood 81:1558-1566, 1993) or by Deb et al. (J. Virology 66:6164-6170, 1992).

Burns et al. teach the preparation of a pHLA A2-CAT116 plasmid comprising a minimal HLA A2 promoter having CCAAT box and TATA box motifs operably linked to a CAT gene (see Fig. 1 and Materials and Methods). Burns et al. further teach that the pHLA A2-CAT116 plasmid is transfected in Jurkat cells (page 1560, col. 1, section "Transfection"). A bacterial chloramphenicol acetyltransferase (CAT) gene product is an antigen since it is capable of eliciting an immunological response in a host.

Deb et al. disclose a plamid comprising a minimal human proliferating cell antigen (PCNA) promoter with a TATA box alone operably linked to a CAT gene (see Fig. 6) for transfection in Hela cells. A bacterial chloramphenicol acetyltransferase (CAT) gene product is an antigen since it is capable of eliciting an immunological response in a host.

Accordingly, Burns et al. and Deb et al. anticipate the instant claims.

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being unpatentable over Laube et al. (Human Gene Ther. 5:853-862, 1994; Cited previously).

The claims are drawn to a method of obtaining expression in mammalian cells of an antigen of interest, and wherein the method comprises *ex vivo* deliverance into cells taken from a subject a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the polypeptide. It is noted that as recited in

the claims, a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen is not limited to a nucleic acid construct consists of a minimal promoter sequence operably linked to a coding sequence for an antigen as contemplated by Applicant because of the opening language "comprising". As such, the claims also read over a nucleic acid construct containing other regulatory sequences including enhancers in addition to a "minimal promoter". For this reason, the following rejection is applied.

Laube et al. disclose *ex vivo* transduction of autologous non-human primate rhesus monkey fibroblasts *ex vivo* transduction of autologous non-human primate rhesus monkey fibroblasts derived from skin biopsies with a retroviral vector encoding HIV-1 IIIB ENV/REV proteins, followed by the readministration of retroviral vector-transduced fibroblasts into the animals to generate cytotoxic T lymphocyte and antibody responses (See abstract). The retroviral vector contains other regulatory elements in addition to a minimal promoter for the expression of HIV-1 IIIB ENV/REV proteins.

Accordingly, Laube et al. anticipate the instant claims.

Claims 1-4, 7-8, 11-17, 20-23 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Fynan et al. (Proc. Natl. Acad. Sci. 90:11478-11482, 1993; IDS).

The claims are directed to a method of obtaining expression in mammalian cells of an antigen of interest, which method comprises transferring into said cells a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said coding sequence is expressed in said

mammalian cells, coated particles comprising carrier particles coated with the same nucleic acid construct, a particle accelerating device loaded with the same coated particles and the same nucleic acid construct. It is noted that as recited in the claims, a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen is not limited to a nucleic acid construct consists of a minimal promoter sequence operably linked to a coding sequence for an antigen as contemplated by Applicant because of the opening language "comprising". With respect to claims 13-14 and 21-22, the phrases "consisting essentially of" and "a functional variant thereof" also do not limit the claims only to a nucleic acid construct consists of a minimal promoter sequence wherein said minimal promoter sequence is a human cytomegalovirus immediate early promoter sequence, a pseudorabies virus early promoter region or a simian cytomegalovirus immediate early promoter sequence because they are open-language phrases. As defined by the instant specification, a functional variant sequence may vary from a native promoter sequence by one or more base substitutions, deletions or insertions (page 10, lines 27-28). As such, the following rejection is applied.

Fynan et al. disclose the preparation of a plasmid DNA comprising a CMV immediate early promoter (containing a minimal promoter) operably linked to a sequence encoding hemagglutininin subtype 1 or subtype 7 antigen, in saline or in coated gold beads for induction of immune responses in murine and avian influenza virus models via gene gun delivery (see the entire article, particularly the abstract, Fig. 1

and Table 4). Accordingly, the instant claims as written encompass the teachings of Fynan et al.

Therefore, Fynan et al. anticipate the instant claims.

Claims 1-3, 7, 12-14 and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Hobart et al. (U.S. Patent No. 5,891,718).

Hobart et al. teach the preparation of a bicistronic eukaryotic expression vector comprising a single transcription unit under the control of a tetracycline-controlled activator-responsive promoter, said unit comprising a first cistron encoding a desired gene product (including an immunogen that stimulates an immune response in a host vertebrate) and a second cistron encoding said tetracycline-controlled activator, and an internal ribosome entry site position between said cistron. An exemplary plasmid vector is VR1370, a nuclear localized tetracycline-controlled activator dependent expression vector having a CAT coding sequence positioned downstream of the seven repeated tetracycline operator sequences, the –53 to +1 hCMV-IE gene TATA box (minimal promoter), and the 944 base hCMV-IE gene 5-prime untranslated region and intron A sequence downstream of said minimal promoter (col. 13, line 29 continues to line 64 of col. 14, and Fig. 1D). The CAT coding sequence is followed immediately by the encephalomyocarditis virus CAP independnt translational enhacer sequene, an internal translational control element able to effect independnt translation of the downstream nuclear localized tetracycline-controlled activator coding sequence on this bicistronic mRNA. Hobart et al. further teach that VR 1370 plasmid is injected into mouse muscle

tissue of animals treated with or without tetracycline and CAT expression is measured over seven days. The results indicated the expression of CAT using the single plasmid construct can be more tightly regulated with tetracycline relative to that achieved in the two plasmid vector system known in the art. Hobart et al. further stated that "Such results indicate that coding sequences carried by these plasmid DNAs can be regulated to deliver desired levels of proteins *in vivo* for the purpose of gene therapy and gene immunization" (col. 14, lines 30-33). The teachings of Hobart et al. meet the limitations of the instant claims. Therefore, Hobart et al. anticipate the instant claimed invention.

Claim Rejections - 35 USC § 103

Claims 1-4, 7-8, 11, 15-17 and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Hobart et al. (U.S. Patent No. 5,891,718) in view of Johnston et al. (U.S. Patent No. 6,194,389; IDS, AK-1).

Hobart et al. teach the preparation of a bicistronic eukaryotic expression vector comprising a single transcription unit under the control of a tetracycline-controlled activator-responsive promoter, said unit comprising a first cistron encoding a desired gene product (including an immunogen that stimulates an immune response in a host vertebrate) and a second cistron encoding said tetracycline-controlled activator, and an internal ribosome entry site position between said cistron. An exemplary plasmid vector is VR1370, a nuclear localized tetracycline-controlled activator dependent expression vector having a CAT coding sequence positioned downstream of the seven repeated tetracycline operator sequences, the –53 to +1 hCMV-IE gene TATA box (minimal

promoter), and the 944 base hCMV-IE gene 5-prime untranslated region and intron A sequence downstream of said minimal promoter (col. 13, line 29 continues to line 64 of col. 14, and Fig. 1D). The CAT coding sequence is followed immediately by the encephalomyocarditis virus CAP independent translational enhancer sequence, an internal translational control element able to effect independent translation of the downstream nuclear localized tetracycline-controlled activator coding sequence on this bicistronic mRNA. Hobart et al. further teach that VR 1370 plasmid is injected into mouse muscle tissue of animals treated with or without tetracycline and CAT expression is measured over seven days. The results indicated the expression of CAT using the single plasmid construct can be more tightly regulated with tetracycline relative to that achieved in the two plasmid vector system known in the art. Hobart et al. further stated that "Such results indicate that coding sequences carried by these plasmid DNAs can be regulated to deliver desired levels of proteins *in vivo* for the purpose of gene therapy and gene immunization" (col. 14, lines 30-33). Hobart et al. do not specifically teach that the bicistronic eukaryotic expression vector to be coated with a carrier, or specifically teach an immunogen is an antigen of a viral, bacterial, parasite or fungal pathogen.

However, at the filing date of the present application, Johnston et al. disclose a method for obtaining a protective immune response in a vertebrate subject by *in situ* microprojectile bombardment by providing microprojectiles carrying a DNA sequence comprising in the 5' to 3' direction a regulatory element functional in the tissue cells and a gene positioned downstream of the regulatory element and under the transcriptional

control thereof, the gene coding for a protective immune response-producing protein or polypeptide, wherein the microprojectiles comprise a material selected from the group consisting of metal (gold, tungsten, iridium), glass, silica, ice , polyethylene, polycarbonate, graphite and diamond; then accelerating the microprojectiles at the subject using a microprojectile acceleration cell transformation apparatus (See abstract, the claims and particularly col. 5 and 6). Johnston et al. teach that the regulatory sequences which may be used to provide transcriptional control of the gene in the polynucleic acid sequence are generally promoters which are operable in the target tissue cells, and that other regulatory elements which may optionally be incorportated into the polynucleic acid sequence include enhancers, termination sequences and others (col. 5, lines 42-45 and lines 65-67). The polynucleic acid sequence carried by the microprojectile is a recombinant construct of a gene and a regulatory element, which can be in the form of a plasmid (col. 4, lines 37-51). Furthermore, exemplary of genes that code for proteins or peptides which produce an immune response are genes encoding for subunit vaccines against enteroviruses, surface antigen of the hepatitis B (col. 5, lines 4-14).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan at the filing date of the present application to use the bicistronic eukaryotic expression vector of Hobart et al. in the form of a DNA coated carrier for genetic immunization of a subject via particle-mediated bombardment technique as taught by Johnston et al. One of ordinary skilled artisan would have been motivated to carry out the above modification because with the bicistronic eukaryotic expression

vector described by Hobart et al., one of ordinary skilled artisan would be able to regulate the delivery of the desired levels of proteins *in vivo* for the purpose of gene immunization to obtain the desired immune responses (Hobart et al., col. 14, lines 30-33). One of ordinary skilled artisan would have a reasonable expectation of success since the regulation delivery of CAT gene under the control of tetracycline has been demonstrated in mice by Hobart et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Quang Nguyen, Ph.D.

DAVE NGUYEN
PRIMARY EXAMINER